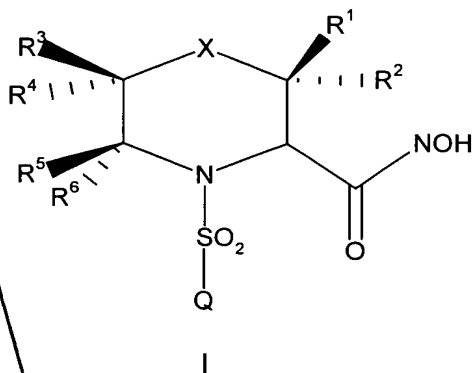


CLAIMS

1. A compound of the formula



or the pharmaceutically acceptable salt thereof, wherein

5 X is oxygen, sulfur, SO, SO₂ or NR⁷;

R¹, R², R³, R⁵ and R⁶ are selected from the group consisting of hydrogen, hydroxy, NH₂, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₂-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₂-C₉)heteroaryl(C₂-C₆)alkynyl, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, perfluoro(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acyl, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-;

15 wherein said (C₁-C₆)alkyl is optionally substituted by one or two groups selected from (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, trifluoromethyl, halo, -CN, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, hydroxy, piperazinyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino or [(C₁-C₆)alkyl]₂amino;

25 R⁷ is hydrogen; (C₁-C₆)alkyl optionally substituted by one or more of hydroxy, -CN, (C₁-C₆)alkylamino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acyl, (C₁-C₆)acylamino, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-; (C₆-C₁₀)arylsulfonyl; (C₁-C₆)alkylsulfonyl; (C₁-C₆)alkyl-NH-(C=O)-; (C₁-C₆)alkoxy-

(C=O)-; (C₁-C₆)alkyl-(C=O)-; [(C₁-C₆)alkyl]₂-N-(C=O)-; or (R⁸R⁹N)-(C=O) where R⁸ and R⁹ are taken together with the nitrogen that they are attached to form a ring selected from azetidiny, pyrrolidiny, piperidiny, morpholiny and thiomorphonyl;

Q is (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, wherein each of said (C₆-C₁₀)aryl or (C₂-C₉)heteroaryl groups may optionally be substituted by one or more substituents, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring independently selected from the group consisting of halo, -CN, (C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-[NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, (C₁-C₆)alkyl-SO₂-[N-(C₁-C₆)alkyl]-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₃-, (C₁-C₆)alkyl-SO₃-, phenyl, phenyl(C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₉)heterocycloalkyl, and (C₂-C₉)heteroaryl;

with the proviso that when X is SO or SO₂, and R³ and R⁴ are a substituent comprising a heteroatom, the heteroatom cannot be bonded to the ring;

and with the proviso that at least one of R¹-R⁶ must be (C₁-C₆)alkyl;

and with the proviso that when X is oxygen or sulfur and R³-R⁶ are each hydrogen then R¹ and R² cannot both be methyl.

2. A compound according to claim 1, wherein X is >NR⁷, sulfur or oxygen.

3. A compound according to claim 1, wherein Q is (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituent is selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

4. A compound according to claim 1, wherein Q is (C₆-C₁₀)arylmethoxy(C₆-C₁₀)aryl, (C₆-C₁₀)arylmethoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroarylmethoxy(C₆-C₁₀)aryl or (C₂-

C₉)heteroaryl methoxy(C₂-C₉)heteroaryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituent is selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

5 5. A compound according to claim 1, wherein Q is optionally substituted (C₆-C₁₀)arylmethoxyphenyl, pyridylmethoxyphenyl, furylmethoxyphenyl, pyrolylmethoxyphenyl, thienylmethoxyphenyl, isothiazolylmethoxyphenyl, imidazolylmethoxyphenyl, benzimidazolylmethoxyphenyl, tetrazolylmethoxyphenyl, pyrazinylmethoxyphenyl, pyrimidylmethoxyphenyl, quinolylmethoxyphenyl, isoquinolylmethoxyphenyl, 10 benzofurylmethoxyphenyl, isobenzofurylmethoxyphenyl, benzothienylmethoxyphenyl, pyrazolylmethoxyphenyl, indolylmethoxyphenyl, isoindolylmethoxyphenyl, purinylmethoxyphenyl, carbazolylmethoxyphenyl, isoxazolylmethoxyphenyl, thiazolylmethoxyphenyl, oxazolylmethoxyphenyl, benzthiazolylmethoxyphenyl, benzoxazolylmethoxyphenyl.

15 6. A compound according to claim 1, wherein Q is (C₆-C₁₀)arylmethoxy(C₆)aryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

20 7. A compound according to claim 1, wherein Q is (C₆-C₁₀)arylmethoxy(C₂-C₉)heteroaryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

25 8. A compound according to claim 1, wherein Q is (C₂-C₉)heteroaryl methoxy(C₆)aryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

30 9. A compound according to claim 1, wherein Q is (C₂-C₉)heteroaryl methoxy(C₂-C₉)heteroaryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

10. A compound according to claim 1, wherein R⁴ is hydrogen.

11. A compound according to claim 1, wherein R² or R³ are hydrogen.

12. A compound according to claim 1, wherein at least one of R² or R³ is other than hydrogen.
13. A compound according to claim 1, wherein at least one of R¹-R³ is (C₁-C₆)alkyl.
- 5 14. A compound according to claim 2, wherein at least one of R¹-R³ is (C₁-C₆)alkyl.
15. A compound according to claim 3, wherein at least one of R¹-R³ is (C₁-C₆)alkyl.
16. A compound according to claim 1, wherein at least one of R¹-R³ is methyl.
- 10 17. A compound according to claim 2, wherein at least one of R¹-R³ is methyl.
18. A compound according to claim 3, wherein at least one of R¹-R³ is methyl.
19. A compound according to claim 3, wherein R¹ is (C₁-C₆)alkyl.
20. A compound according to claim 3, wherein R² is (C₁-C₆)alkyl.
21. A compound according to claim 3, wherein R³ is (C₁-C₆)alkyl.
- 15 22. A compound according to claim 3, wherein R⁴ is (C₁-C₆)alkyl.
23. A compound according to claim 1 wherein R¹ and R⁴ are each methyl.
24. A compound according to claim 2 wherein R¹ and R⁴ are each methyl.
25. A compound according to claim 3 wherein R¹ and R⁴ are each methyl.
26. A compound according to claim 1, wherein R¹ and R² are each (C₁-C₆)alkyl.
- 20 27. A compound according to claim 2, wherein R¹ and R² are each (C₁-C₆)alkyl.
28. A compound according to claim 3, wherein R¹ and R² are each (C₁-C₆)alkyl.
29. A compound according to claim 1, wherein R¹ and R² are each methyl.
30. A compound according to claim 2, wherein R¹ and R² are each methyl.
31. A compound according to claim 3, wherein R¹ and R² are each methyl.
- 25 32. A compound according to claim 1 wherein R¹ is methyl and R² is hydrogen;
33. A compound according to claim 1 wherein R¹ is hydrogen and R³ is methyl.
34. A compound according to claim 3, wherein R¹ and R³ are each methyl.
35. A compound according to claim 3, wherein R¹ and R⁴ are each methyl.
36. A compound according to claim 3, wherein R² and R³ are each methyl.
- 30 37. A compound according to claim 3, wherein R² and R⁴ are each methyl.
38. A compound according to claim 3, wherein R³ and R⁴ are each methyl.
39. A compound according to claim 1 wherein X is NR⁷.
40. A compound according to claim 3 wherein X is NR⁷.
41. A compound according to claim 4 wherein X is NR⁷.
- 35 42. A compound according to claim 5 wherein X is NR⁷.

43. A compound according to claim 6 wherein X is NR⁷.
44. A compound according to claim 13 wherein X is NR⁷.
45. A compound according to claim 15 wherein X is NR⁷.
46. A compound according to claim 1 wherein X is NR⁷ and R⁷ is (C₁-C₆)alkyl.
5 47. A compound according to claim 1 wherein X is NR⁷ and R⁷ is (C₁-C₆)alkylsulfonyl.
48. A compound according to claim 1 wherein X is NR⁷ and R⁷ is (C₆-C₁₀)arylsulfonyl.
49. A compound according to claim 1 wherein X is NR⁷ and R⁷ is [(C₁-C₆)alkyl]₂N-(C=O)- or (C₁-C₆)alkylNH-(C=O)-.
10 50. A compound according to claim 1 wherein X is NR⁷ and R⁷ is (C₁-C₆)alkyl(C=O)-.
51. A compound according to claim 1, wherein said compound is selected from the group consisting of:
15 (2S,3S)-4-[4-(3,5-difluoro-benzyloxy)-benzenesulfonyl]-2-methyl-thiomorpholine-3-carboxylic acid hydroxyamide;
(2S,3S)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2-methyl-thiomorpholine-3-carboxylic acid hydroxyamide;
(2S,3R,6S)-2,6-dimethyl-4-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-morpholine-3-
20 carboxylic acid hydroxyamide;
4-(4-benzyloxy-benzenesulfonyl)-2-methyl-morpholine-3-carboxylic acid hydroxyamide;
(2S,3R,6S)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
25 (3R,6S)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2,2,6-trimethyl-morpholine-3-carboxylic acid hydroxyamide;
(2S,3R,6S)-6-ethyl-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2-methyl-morpholine-3-carboxylic acid hydroxyamide;
(2R,3R,6S)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
30 (2R,3R,6R)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
(2S,3R,6S)-2,6-dimethyl-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

- (2*S*,3*R*,6*S*)-2,6-dimethyl-4-[4-(pyridin-2-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-2,6-dimethyl-4-[4-(pyridin-3-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;
- 5 (2*S*,3*R*,6*S*)-2,6-dimethyl-4-[4-(2-methyl-pyridin-3-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;
- (3*R*,6*S*)-2,2,6-trimethyl-4-[4-(2-trifluoromethyl-benzyloxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;
- (2*S*,3*R*)-2,6,6-trimethyl-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-morpholine-3-
- 10 carboxylic acid hydroxyamide;
- (3*R*,6*S*)-2,2,6-trimethyl-4-[4-(2-methyl-pyridin-3-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-[4-(2,5-dimethyl-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-
- 15 carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-4-[4-(3,5-difluoro-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-4-[4-(3-methoxy-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-
- 20 carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-4-[4-(5-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-4-[4-(furan-3-ylmethoxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-
- 25 carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-4-[4-(2-fluoro-3-methyl-benzyloxy)-benzenesulfonyl]-2,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
- (2*S*,3*R*)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-2,6,6-trimethyl-morpholine-3-
- 30 carboxylic acid hydroxyamide;
- (3*R*)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-6,6-dimethyl-morpholine-3-carboxylic acid hydroxyamide;
- (3*R*)-6,6-dimethyl-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-morpholine-3-
- carboxylic acid hydroxyamide;
- (3*R*)-6,6-dimethyl-4-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-morpholine-3-
- carboxylic acid hydroxyamide;
- (2*S*,3*R*,6*S*)-4-(4-cyclohexylmethoxy-benzenesulfonyl)-2,6-dimethyl-morpholine-3-
- carboxylic acid hydroxyamide;

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(3R,6S)-4-[4-(2,5-dimethyl-benzyloxy)-benzenesulfonyl]-2,2,6-trimethyl-morpholine-3-carboxylic acid hydroxyamide;

(2S,3R)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-6-methoxymethyl-2-methyl-morpholine-3-carboxylic acid hydroxyamide;

5 (2S,3R,6S)-4-[4-(3-chloro-benzyloxy)-benzenesulfonyl]-6-[(ethyl-methyl-amino)-methyl]-2-methyl-morpholine-3-carboxylic acid hydroxyamide;

(2S,3R)-4-[4-(3-chloro-benzyloxy)-benzenesulfonyl]-6-methoxy-2-methyl-morpholine-3-carboxylic acid hydroxyamide;

10 (2S,3R,6R)-4-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-6-hydroxymethyl-2-methyl-morpholine-3-carboxylic acid hydroxyamide.

52. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of a matrix metalloproteinase in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

15 53. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of a mammalian reprotolysin in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

20 54. A pharmaceutical composition for the treatment of arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral
25 ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring,
30 scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

55. A method for the inhibition of the the cellular production/release of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said
35 mammal an effective amount of a compound of claim 1.

15 57. A method of inhibiting the cleavage of TNF- α from cell membranes in a mammal comprising administering to such mammal an effective amount of compound according to claim 1 that inhibits the TNF- α proteolytic activity of TACE.

59. A method for treating a mammal having a disease characterized by an unregulated cellular production/release of TNF- α , comprising administering to the mammal a composition comprising an amount of a compound according to claim 1 that effectively inhibits the TNF- α proteolytic activity of TACE.

61. A method of inhibiting the cleavage of TNF- α from cell membranes without inhibiting MMP-1 in a mammal comprising administering to such mammal an effective amount of a hydroxamic acid compound that inhibits the TNF- α proteolytic activity of TACE without inhibiting MMP-1.

62. A method for treating a mammal having a disease characterized by an overproduction of soluble TNF- α , comprising administering to the mammal a composition

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71. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of an Aggrecanase inhibitor, wherein said Aggrecanase inhibitor selectively inhibits Aggrecanase at least ten times as well as MMP-1.

72. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of an Aggrecanase inhibitor, wherein said Aggrecanase inhibitor selectively inhibits Aggrecanase and MMP-13 in preference to MMP-1.

5 73. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of an Aggrecanase inhibitor, wherein said Aggrecanase inhibitor selectively inhibits Aggrecanase and MMP-13 at least ten times as well as MMP-1.

74. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of a hydroxamic acid Aggrecanase inhibitor, wherein said hydroxamic acid Aggrecanase inhibitor selectively inhibits Aggrecanase and MMP-13 in
10 preference to MMP-1.

75. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of a hydroxamic acid Aggrecanase inhibitor, wherein said hydroxamic acid Aggrecanase inhibitor selectively inhibits Aggrecanase and MMP-13 at least
15 ten times as well as MMP-1.

76. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of an agent, wherein said agent selectively inhibits Aggrecanase and TACE in preference to MMP-1.

77. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of a hydroxamic acid, wherein said hydroxamic acid selectively
20 inhibits Aggrecanase and TACE at least ten times as well as MMP-1.

78. A method of treating arthritis in a mammal, comprising administering to such mammal an effective amount of an agent, wherein said agent selectively inhibits Aggrecanase, MMP-13 and TACE in preference to MMP-1.

79. A method of treating arthritis in a mammal, comprising administering to such
25 mammal an effective amount of a hydroxamic acid, wherein said hydroxamic acid selectively inhibits Aggrecanase, MMP-13 and TACE at least ten times as well as MMP-1

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